PATENT
Attorney Docket No. 09210.0004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Burton G. CHRISTENSEN et al.	)	Group Art Unit: 1639
	)	
Application No.: 09/457,926	)	Examiner: Mark Shibuya
	)	
Filed: December 8, 1999	)	
	)	
For: NOVEL ANTIBACTERIAL AGENTS	)	Confirmation No.: 8221

Attention: Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPEAL BRIEF UNDER BOARD RULE § 41.37

In support of the Notice of Appeal filed May 19, 2006, and further to Board Rule 41.37, Appellants present this brief and enclose herewith a check for the fee of $500.00 required under 37 C.F.R. § 1.17(c).

This Appeal responds to the November 21, 2005, final rejection of claims 41, 43, 49-51, and 53-55.

If any additional fees are required or if the enclosed payment is insufficient, Appellants requests that the required fees be charged to Deposit Account No. 06-0916.

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I. Real Party In Interest

The real party in interest in this appeal is THERAVANCE, INC., a corporation duly organized under and pursuant to the laws of Delaware, and having its principal place of business at 901 Gateway Boulevard, South San Francisco, California 94080.

II. Status Of Claims

Claims 41-46, 49-51, 53-55, 57 and 58 are subject of this appeal. Claims 42, 44-46, 57 and 58 have been withdrawn from consideration by the Examiner but are not cancelled. Claims 41, 43, 49-51, and 53-55 have been rejected. Claims 1-40, 47, 48, 52 and 56 have been cancelled. No claims have been allowed.

III. Status Of Amendments

No amendments have been filed subsequent to the final rejection.

IV. Summary Of Claimed Subject Matter

Appellants' presently claimed invention is directed to novel multi-binding compounds that are antibacterial agents. *See* Specification, at p. 1, lines 2-3. As discussed in the specification, antibacterial agents are important weapons in the fight against pathogenic bacteria. Of late, however, strains of bacteria have emerged that are highly resistant to present day antibacterial agents. Accordingly, it is highly desirable to discover antibacterial agents that are active against a broad spectrum of bacteria, demonstrate high activity and selectivity, but are of low toxicity. *Id.* at p. 2, lines 17-23.

The present invention is directed to novel antibacterial agents. More specifically, the claimed invention is directed to novel chemical compounds having a vancomycin-like moiety and a beta-lactam moiety covalently linked together at specifically defined points of attachment through a linking moiety. The novel chemical compounds of the present claims can be illustrated by the formula:

L'-X-L"

where L' represents the beta-lactam moiety, L" represents the vancomycin-like moiety and X represents the linking group. In the compounds as presently claimed, each moiety is specifically defined and the points at which each moiety is attached to the other moieties are also specifically defined. *Id.* at p. 39, line 18 to page 48, line 8.

The presently claimed invention is also directed to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of any of the claimed compounds. *Id.* At p. 112, line 31 to p. 115, line 14. The compounds and

pharmaceutical compositions of this invention are useful as antibacterial agents. *Id.* At p. 112, lines 15-29.

Independent claim 41 is directed to a compound of the formula:

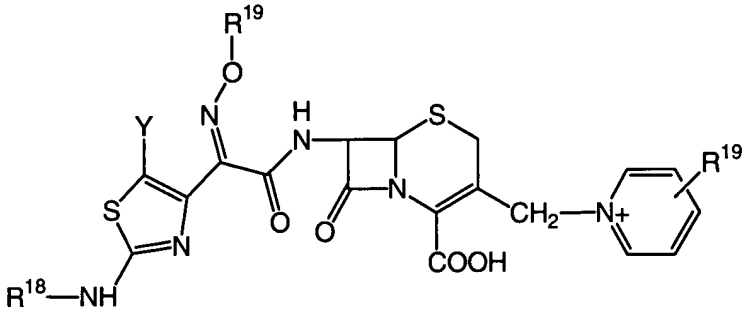
L'-X'-L"

or pharmaceutically acceptable salts thereof, wherein L' is a specifically-defined beta-lactam moiety, X' is a specifically-defined linker, and L" is an optionally substituted vancomycin moiety (or an aglycone derivative thereof), which is attached to the linker at positions selected from the group consisting of the carboxy terminus, the amino terminus, the dihydroxyphenyl ring, the saccharide amino group, and the aglycone hydroxy terminus. *Id.* at p. 39, line 18 to page 48, line 8.

Independent claim 53 is also directed to a compound of the formula:

L'-X'-L"

wherein L' is a moiety of the formula:



X' is a specifically-defined linker, and L" is a vancomycin moiety, which is attached to the linker at positions selected from the group consisting of the carboxy terminus, the amino terminus, the dihydroxyphenyl ring, the saccharide amino group of the vancomycin moiety. *Id.* at pp. 39, line 18 to page 48, line 8 and specifically, p. 43, line 10, p. 45, line 1.

V. Grounds of Rejection

Claims 41, 43, 49-51 and 53-55 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over:

(1) U.S. Patent No. 5,693,791, issued on December 2, 1997 to William L. Truett ("Truett I"); in view of:

(2) U.S. Patent No. 6,437,119, issued on August 20, 2002 to William L. Truett ("Truett II");

(3) Michael Boeckh et al., *Antimicrob. Agents Chemother.*, 1988, 32(1) 92-95 ("Boeckh");

(4) M. Renoud Grappin et al., *Antiviral Chem. and Chemotherapy*, 1998, 9(3), 205-223 ("Renoud-Grappin"); and

(5) Thomas Staroske et al., *Tet. Lett.* 1998, 39, 4917-4920 ("Staroske").

VI. Argument

A. Truett I in View of Truett II, Boeckh, Renoud-Grappin and Staroske Does Not Render Claims 41, 43, 49-51 and 53-55 Obvious

1. The Office's Rejection

The Office's November 21, 2005, Final Office Action rejects claims 41, 43, 49-51, and 53-55 under 35 U.S.C. § 103(a) over Truett I in view of Truett II, Boeckh, Renoud-Grappin, and Staroske. *See* Final Office Action, pp. 2-3.

In the rejection, the Office states that Truett I teaches the linking of diverse antibiotic moieties via difunctional compounds in order to prepare dimers having the structure A-L-B, where A and B are various antibiotic moieties and L represents a variety of linkers. *Id.* at p. 3. Additionally, the Office states that Truett I teaches "that the linkage of two antibiotic moieties can create compounds of new activity." *Id.* Furthermore, the Office states that Truett I "teaches a dimeric compound where one of the antibiotic moieties is ceftazidime, . . . [which is] a beta-lactam antibiotic that reads on the elected species found in claim 53." *Id.* Notably, however, the Office admits that Truett I "lacks the teaching of linking vancomycin with ceftazidime." *Id.*

To compensate for the deficiency in Truett I, the Office relies upon a combination of four other references: Truett II; Boeckh; Renoud-Grappin; and Staroske. According to the Office, Truett II teaches that "making and using compounds having three antibiotic functionalities linked together, where a quinolone derivative is linked to a beta-lactam, which, in turn, is linked to vancomycin." *Id.* at p. 5. Based on this disclosure, the Office concludes that Truett II "teaches linking a beta-lactam antibiotic to vancomycin in an antibiotic compound." *Id.*

The Office states that Boeckh teaches that it "was well known in the art at the time of filing to use combination therapy with vancomycin and ceftazidime," and, thus, "pharmaceutical

compositions of the drugs are well known." *Id.* The Office relies on Renoud-Grappin for the suggestion that "one way to achieve effective combination therapy is to covalently link two different drugs," and that such a combination of drugs could "prevent the emergence of drug-resistant virus strains." *Id.* Importantly, the Office admits that Renoud-Grappin deals with compounds that are "anti-virals and not antibiotics." *Id.* Finally, the Office relies on Staroske to disclose "dimeric vancomycin compounds [which] exhibit improved antibacterial activity...." *Id.*

Based on the combination of all five of these references, the Office contends that:

> [I]t would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to link vancomycin and ceftazidime, based on the teaching of [Truett I], concerning the linking of diverse antibiotic moieties, and [Truett II], where vancomycin and beta-lactam antibiotics are linked as part of a linked, three antibiotic compound, combined with the teaching of [Boeckh] to perform combination therapy using the drugs, the teaching of [Renoud-Grappin] concerning linking drugs to perform combination therapy and the teaching of [Staroske] concerning vancomycin dimers linked through the amino and carboxy terminus . . . .
>
> One of ordinary skill would have been motivated to covalently link vancomycin with ceftazidime to create a broad spectrum antibiotic compound to fight antibiotic resistant strains. Furthermore, it would have been obvious . . . to have combined the compounds taught by the references . . . because said compounds are used for a common purpose, i.e., the treatment of bacterial infection.
>
> One of ordinary skill would also have had a reasonable expectation of success based on the fact that the references of [Truett I] and [Truett II] and [Staroske] teach linking chemistry for vancomycin and beta-lactam compounds.

Id. at p. 4.

2. The Office Has Failed to Establish a Prima Facie Case of Obviousness

Several basic factual inquires must be made in order to determine the obviousness or non-obviousness of claims of a patent application under 35 U.S.C. § 103. These factual inquiries, set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 U.S.P.Q. 459, 467 (1966), require the Office to:

(1) Determine the scope and content of the prior art;

(2) Ascertain the differences between the prior art and the claims in issue;

(3) Resolve the level of ordinary skill in the pertinent art; and

(4) Evaluate evidence of secondary considerations.

The obviousness or nonobviousness of the claimed invention is then evaluated in view of the results of these inquiries. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467. The M.P.E.P. sets forth the following tenets of patent law that must be adhered to when making an obviousness rejection:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined.

M.P.E.P. § 2141 (citing *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n. 5, 229 U.S.P.Q. 182, 187 n. 5 (Fed. Cir. 1986)).

Thus, in order to carry the initial burden of establishing a *prima facie* case of obviousness that satisfies the *Graham* standard, the Office must show (1) that all elements are disclosed by the prior art references, (2) that there exists some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings, and (3) that there is a reasonable expectation of success. *See* M.P.E.P. § 2143.

3. The References Failed To Provide a Suggestion or Motivation To Combine an Modify

The Office can meet the burden of establishing a *prima facie* case of obviousness "only by showing some **objective teaching** in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988) (internal citations omitted) (emphasis added). The Federal Circuit reaffirmed the Office's high burden to establish a *prima facie* case of obviousness in *In re Lee*, where the Federal Circuit explained that

> **[t]he need for specificity pervades this authority**... the examiner can satisfy the burden of showing obviousness of the combination **only by showing some objective teaching** in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.

277 F.3d 1338, 1433, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002) (internal citations and quotation omitted) (emphasis added). Moreover, "[t]o establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making **the specific combination** that was made by the applicant." *In re Kotzab*, 217 F.3d 1365, 1370, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir, 2000) (emphasis added).

Here, the references as a whole fail to provide a "motivation, suggestion or teaching of the desirability of making the specific combination that was made" by Appellants. As discussed in greater detail below, the Office's proposal to modify Truett II would destroy the intended function of its disclosed compounds, thereby eliminating any motivation to modify. Further, Truett I discloses 69 different antibiotic compounds without any guidance to select one compound above all else. And the Office has not provide any basis to support its contention that one skilled in the art would be motivated to select ceftazidime out of the 69 specifically named compounds disclosed in the reference. Finally, Broeckh, Renoud-Grappin, and Staroske do not cure the deficiencies in Truett I and II.

Before turning to the substantive teachings of the prior art, Appellants note the Office contends that in the June 28, 2005 response, Appellants argued each of the cited references individually when the rejection was based on the combination of the references as a whole. *See* Final Office Action at 7. Appellants respectfully disagree. Adequately addressing the deficiencies in the references cited by the Office in support of its obviousness rejection requires a discussion of each individual reference, pointing out why the reference, when considered in combination with the other cited reference, fails to establish a prima facie case of obviousness. Accordingly, Appellants' arguments must fully address the teachings found in each of the cited references in order to ascertain whether such teachings provide the requisite motivation to combine the references in the manner suggested by the Office.

4. Modifying Truett II as suggested by the Office would destroy the intended function of the disclosed compounds

The Office acknowledges that Truett II teaches "making and using compounds having **three antibiotic functionalities linked together**," where two of the three components are a

beta-lactam antibiotic and vancomycin. Final Office Action at p. 5. The Office also contends that Truett II "teaches linking a beta-lactam antibiotic to vancomycin in an antibiotic compound." *Id.* For the reasons discussed below, Appellants respectfully contend that the Office has made too broad an assertion regarding the teachings of Truett II, and submit that Truett II provides no motivation to link only a beta-lactam antibiotic to vancomycin.

Truett II is specifically directed to the formation of "a single compound" comprised of two antibiotics (quinolone and beta-lactam antibiotics). *See* Truett II, col. 1, lines 13-20. The reference also discloses that a third antibiotic, such as vancomycin, can be added to form a single compound. *Id.* Thus, considering Truett II as a whole, the reference would, at best, motivate one of skill in the art to link a beta-lactam antibiotic to vancomycin *only* when a third quinolone antibiotic is part of the composition. Read as a whole, Truett II does not generally teach "linking a beta-lactam antibiotic to vancomycin" as alleged by the Office.

Making modifications based on the disclosure of Truett II would require substantially redesigning the disclosed compounds in such a way that the intended function of the disclosed compounds would be destroyed. Throughout Truett II, the reference emphasizes the value of the three-component antibiotic. *See* col. 1, lines 22-27 ("**The value of a composition wherein a trio of individual antibiotics are joined** is that the bacterial infective agent will be simultaneously be attached by agents which are known to attack the cell-wall producing enzyme of the bacteria . . . .") (emphasis added); col. 1, lines 28-31 ("The value of this composition of three antibiotic functional types . . . ."). Further, the only example in Truett II is directed to the three-component antibiotic. *Id.* at col. 24, line 50 to col. 25, line 43. Contrary to the Office's assertion, there is simply no disclosure in Truett II of a two-component antibiotic compound composed of a beta-lactam antibiotic and vancomycin, let alone a disclosure that such a

combination would be effective. Clearly, Truett II views the value of its antibiotic composition lies in its combination of three antibiotic compounds.

The Federal Circuit and its predecessor have consistently held that "[a] proposed modification [is] inappropriate for an obviousness inquiry when the modification render[s] the prior art reference inoperable for its intended purpose." *In re Fritch*, 972 F.2d 1260, 1265 n.12, 23 U.S.P.Q.2d 1780, 1783 n. 12 (Fed. Cir. 1992); *In re Ratti*, 270 F.2d 810, 813, 123 U.S.P.Q. 349, 352 (C.C.P.A. 1959) (holding the suggested combination of references improper under § 103 because it "would require a substantial reconstruction and redesign of the elements shown in [a prior art reference] as well as a change in the basic principles under which [that reference's] construction was designed to operate").

Here, because the alleged success in using an antibiotic comprising a beta-lactam antibiotic and vancomycin is derived **only** with the inclusion of a quinolone antibiotic, there is no evidence that linking a beta-lactam antibiotic with vancomycin will work for its intended purpose. Moreover, making such a modification completely changes the basic principle that the three-component antibiotic in Truett II was designed to operate. For this reason, the reference provides no motivation to link only a beta-lactam antibiotic with vancomycin.

5. Truett II teaches away from combining only ceftazidime and vancomycin

As discussed above, Truett II discloses that the three-component antibiotic is suitable for treatment of a variety of bacterial infections. *See* Truett II, col. 3, lines 41-44. And in terms of forming a two-component antibiotic, Truett II teaches linking a quinolone antibiotic to a beta-lactam antibiotic. The reference never suggests linking only beta-lactam with vancomycin. And the only instance where a beta-lactam antibiotic is linked with vancomycin is in combination

with a quinolone antibiotic. Considering the disclosure of Truett II as a whole, the reference not only does not suggest linking only a beta-lactam antibiotic with vancomycin, but actually teaches away from such a combination by requiring the presence of a quinolone moiety. Because Truett II teaches away from forming a two-component antibiotic comprised of a beta-lactam and vancomycin, the reference fails to provide any motivation to modify its teaching to reach the claimed invention.

6. The Office provides no basis to select ceftazidime from the 69 named compounds disclosed in Truett I

The Office relies on Truett I for the general disclosure "that the linkage of two antibiotic moieties can create compounds of new activity." Final Office Action at p. 4. Truett I is also relied on for the proposition that it "teaches a dimeric compound where one of the antibiotic moieties is ceftazidime, . . . [which is] a beta-lactam antibiotic that reads on the elected species found in claim 53." *Id.* The Office acknowledges, however, that Truett I does not disclose linking ceftazidime with vancomycin. As emphasized above, when making an obviousness evaluation, each reference must be considered as a whole. *See Hodash*, 786 F.2d at 1143. Here, the Office focuses its attention on ceftazidime based solely on the compounds disclosure in Appellants' invention. This clear use of hindsight construction cannot support an obviousness rejection.

When considering the reference as a whole, one of ordinary skill in the art would appreciate that Truett I discloses a large number of antibiotic compounds that may be linked together according to the invention of Truett I. Appellants initially note that none of the antibiotic compounds is vancomycin. In fact, Truett I discloses **nine general classes** of antibiotic compounds and **69 specifically named compounds** within those classes that may be

linked together. *See* Truett I, col. 1, line 46 through col. 6, lines 27. Not only does Truett I disclose 69 specifically named compounds within 9 generic classes of antibiotics, the reference fails to provide any suggestion or motivation for selecting one of the 9 classes, let alone a single compound within that class. There is simply no suggestion or motivation to select ceftazidime. Appellants respectfully submit that the Office must provide a basis for the initial selection of a single one of the 69 specific compounds, i.e., ceftazidime, from among all the other antibiotic compounds disclosed in the reference. This, the Office has not done.

The Office asserts that "Truett I teaches and suggests the use of ceftazidime as a member antibiotic of a dimeric compound." Final Office Action at p. 8. The Office specifically relies on Truett I's disclosure of ceftazidime as a cephalosporin of "particular interest," and the reference's disclosure of ceftazidime's chemical structure. *Id.* Based on this disclosure, the Office contends that Truett I "provides ample motivation for the selection of ceftazidime." *Id.* The Office goes on to state that the disclosure of 69 known compounds "does not represent an unreasonable number, in and of itself, to use in the claimed invention of the prior art reference of Truett I." *Id.*

The Office's response only highlights the use of hindsight reasoning to select ceftazidime. Appellants do not dispute that Truett I discloses ceftazidime. But, ceftazidime is only 1 of 17 different cephalosporins "of particular interest" in the reference. *See* Truett I at col. 2, line 59 to col. 3, line 14. Notable also is the fact that Truett I also uses that phrase when discussing sulfonamides, penicillins, and quinolones. *Id.* at col. 2, line 1 to col. 3, line 32. The references repeated use of "particular interest" emphasizes Appellants' contention that no compound, let alone class, is singled out by the reference. Truett I also discloses the chemical structure of the 69 named compounds and all 17 of the cephalosporins disclosed in columns 2-3.

Id. at col. 8, line 55 to col. 22, line 9. Thus, Truett I's disclosure of the chemical structure of ceftazidime does not provide the requisite motivation necessary to select this compound among all others.

Finally, the Office provides no basis to support its contention that the disclosure of 69 known compounds "does not represent an unreasonable number, in and of itself, to use in the claimed invention of the prior art reference of Truett I." Contrary to the Office's assertion, Appellants submit it is unreasonable to select one compound (ceftazidime) out of the 69 compounds disclosed in the reference given that the reference provides absolutely no guidance to select one compound over another. In fact, considering Truett I as a whole, the reference actually supports Appellants' position that ceftazidime is no more important than any other compound of Truett I.

In the face of this limited guidance, and the lack of any disclosure regarding vancomycin, Applicants respectfully submit that one or ordinary skill in the art reading the general teachings of Truett I would have found nothing to motivate or guide them to prepare a compound containing both a beta-lactam and vancomycin composition as proposed by the Office.

In summary, Truett II does not suggest or motivate one skilled in the art to link only ceftazidime and vancomycin because doing so would destroy the basic principle for which the compounds in the reference were designed. Further, by emphasizing particular three-component antibiotics, Truett II teaches away from such a combination. And, as a whole, Truett I provides no suggestion or motivation to select ceftazidime over any of the other 69 compounds disclosed in the reference.

Boeckh, Renoud-Grappin, and Staroske do not cure the deficiencies in Truett I and II. That is, these three references do not provide any motivation to link ceftazidime and

vancomycin. Staroske discloses that vancomycin can be linked to other compounds. But this general disclosure does not provide motivation to link ceftazidime and vancomycin. Renoud-Grappin simply discloses linking two drugs, none of which are antibiotics. This too fails to provide any motivation to link ceftazidime and vancomycin.

Boeckh, while disclosing the combination of ceftazidime and vancomycin as separate compounds, is not directed to linking the two together. In fact, Boeckh specifically discloses that previous studies show "excellent clinical response to the combination of vancomycin and ceftazidime," as separate compounds. *See* Broeckh at 94, right column. One of ordinary skill in the art, considering Broeckh as a whole, would conclude that the reference discloses the use of ceftazidime and vancomycin as separate compounds within a mixture without any apparent disadvantages, including any inconveniences. Accordingly, that skilled artisan would have no motivation to modify Broeckh's composition by linking ceftazidime to vancomycin, as required by the Appellants' invention. *See Winner Int'l Royalty Cor v. Wang*, 202 F.3d 1340, 1349, 53 U.S.P.Q.2d 1580, 1587 (Fed. Cir. 2000) (where the Federal Circuit upheld a finding of no motivation to combine references when there was no apparent disadvantage to using the method disclosed in one of the prior art references.). As such, neither Staroske, Renoud-Grappin, nor Boeckh cure the deficiencies in Truett I and II by motivating one skilled in the art to link ceftazidime and vancomycin.

B. The Office's Additional Remarks in Its Final Office Action Do No Support a Prima Facie Case of Obviousness

In response to Appellants' June 28, 2005 response, the Office contends that "the motivation for using heterodimeric antibiotic compounds of Truett I is closely related and extendable to the heterotrimeric antibiotic compounds of related patent Truett II." Final Office

Action at p. 8. While there may be a general desire in the art to create broad spectrum antibiotics, this general desire alone is not enough to provide motivation to link the two specific antibiotics of the claimed invention (ceftazidime and vancomycin are the selected species). Following the Office's logic, the desire and need for broad spectrum antibiotics would render virtually any new broad spectrum antibiotic obvious. This simply cannot be the standard.

Well settled Federal Circuit precedent requires that the cited references must provide a specific suggestion or motivation to link ceftazidime and vancomycin in a particular manner to arrive at the subject matter of the present claims. *In re Lee*, 277 F.3d at 1433, 61 U.S.P.Q.2d at 1433. The mere fact that both Truett I and II disclose broad spectrum antibiotics composed of either two or three antibiotic agents is not enough to meet the burden of establishing a prima facie case of obviousness. This is because neither reference suggests linking only ceftazidime and vancomycin, let alone linking them in the particular manner of the present claims. The only teaching in either reference is to link ceftazidime and vancomycin **in combination with** a quinolone to create compounds that are structurally quite distinct from those of the present claims. And, removal of the quinolone would destroy the teaching of Truett II. These facts, combined with Broeckh's disclosure that ceftazidime and vancomycin, when combined in a mixture as opposed to linked together, provides an "excellent clinical response," would not direct one skilled in the art to link ceftazidime and vancomycin.

Moreover, the Office has simply taken the position that you can select a beta-lactam moiety from Truett I and combine it with vancomycin from Truett II. This view of Truett I and Truett II is too simplistic and does not take into account the references as a whole. Truett II teaches combining the beta-lactam/quinolone moiety with eight different classes of antibiotics, i.e., tetracyclines, metronidozole, chloramphenicol, clindinamycin, aminoglycosides,

erythromycin, azithiromycin, and vancomycin. *See* Truett II at col. 3, lines 18-28. Thus, in order to attempt to arrive at the presently claimed invention, one of ordinary skill in the art would not only need to select a beta-lactam from Truett I but would also need to select vancomycin from Truett II and then dissect the quinolone moiety from the resulting compounds. Given the vast number of combinations that are possible based on the teachings of Truett I and Truett II, especially when one considers that each moiety may have several possible points of attachment, the number of selections and dissections necessary to attempt to arrive at the presently claimed invention from the teaching of Truett I and Truett II is truly astronomical.

The Office has thus failed to address these specific problems with the combination of references. Other than using hindsight knowledge of the presently claimed invention to pick and choose from Truett I and Truett II, the Office has not explained why one of ordinary skill in the art would have been motivated to modify the teachings to Truett I and Truett II in the manner suggested by the Office.

C. CONCLUSION

For the reasons given above, pending claims 41, 43, 49-51, and 53-55 are allowable and reversal of the Office's rejection is respectfully requested.

To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: July 13, 2006

By: _____
Sanya Sukduang
Reg. No. 46,390

VII. Claims Appendix to Appeal Brief Under Rule 41.37(c)(1)(viii)

Claims 1-40, 47-48, 52, and 56 have been cancelled.

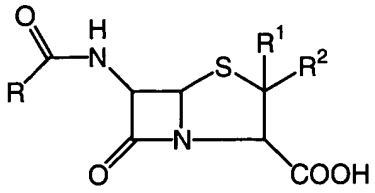
41. (Previously presented) A compound of the formula:

L'–X'–L"

or a pharmaceutically acceptable salt thereof; wherein

L' is a moiety selected from the group consisting of:

(i) a moiety of formula (a):



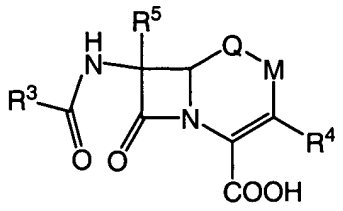
(a)

wherein:

R is selected from the group consisting of substituted alkyl, aryl, aralkyl, and heteroaryl wherein each of said substituents optionally links (a) to the linker via a covalent bond or R is a covalent bond that links (a) to the linker; and

R^1 and R^2 are, independently of each other, alkyl or at least one of R^1 or R^2 is a covalent bond linking (a) to the linker provided that only one of R, R^1 or R^2 links said moiety to said linker;

(ii) a moiety of formula (b):



(b)

wherein:

one of M and Q is O, S, or $-CH_2-$ and the other is $-CH_2-$;

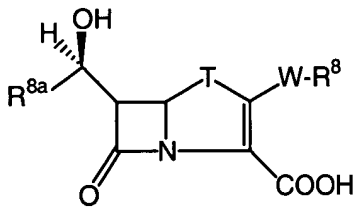
R^3 is selected from the group consisting of substituted alkyl, heteroarylalkyl, aralkyl, heterocyclylalkyl, and $-C(R^6)=NOR^7$, wherein R^6 is aryl, heteroaryl, or substituted alkyl and R^7

is alkyl or substituted alkyl and further wherein each of said substituents optionally links (b) to the linker via a covalent bond or R^3 is a covalent bond that links (b) to the linker; and

R^4 is selected from the group consisting of hydrogen, alkyl, alkenyl, substituted alkenyl, substituted alkyl, halo, heteroarylalkyl, heterocyclylalkyl, $-SR^a$ and $-CH_2SR^a$, where R^a is aryl, heteroaryl, heterocyclyl or cycloalkyl wherein each of said substituents optionally links (b) to the linker or R^4 is a covalent bond that links (b) to the linker provided that only one of said R^3 substituents or covalent bond and R^4 substituents or covalent bond links said moiety to said linker; and

R^5 is selected from the group consisting of hydrogen, hydroxy; and alkoxy;

(iii) a moiety of formula (c):



(c)

wherein:

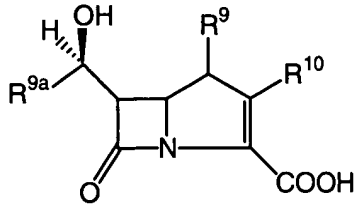
T is S or CH_2,

R^{8a} is alkyl;

W is selected from the group consisting of O, S, $-OCH_2-$, and CH_2; and

R^8 is -(alkylene)-NHC(R^b)=NH where R^b is a covalent bond that links (c) to the linker; or $-W-R^8$ is a covalent bond that links (c) to the linker provided that only one of R^b or $-W-R^8$ binds said moiety to said linker;

(iv) a moiety of formula (d):



(d)

wherein:

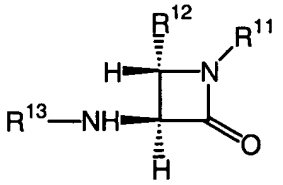
R^9 and R^{9a} are alkyl;

R^{10} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, halo, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl and $-CH_2SR^a$, where R^a is aryl,

heteroaryl, heterocyclyl or cycloalkyl wherein each of said substituents optionally links (d) to the linker or at least one of R^9 and R^{10} is a covalent bond that links (d) to the linker; or

R^9 and R^{10}, together with the carbon atoms to which they are attached, form an aryl, heteroaryl, cycloalkyl, substituted cycloalkyl, or heterocyclyl ring of from 4 to 7 ring atoms wherein one of the ring atoms optionally links (d) to the linker provided that only one of said substituents, ring atoms, R^9 or R^{10} links said moiety to said linker; and

(v) a moiety of formula (e):



(e)

wherein:

R^{11} is selected from the group consisting of $-SO_3H$ or -(alkylene)-COOH;

R^{12} is selected from the group consisting of alkyl, substituted alkyl, haloalkyl, alkoxy, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, substituted cycloalkyl, and heterocyclyl wherein each of said substituents optionally binds (e) to the linker or R^{12} is a covalent bond that links (e) to the linker,

R^{13} is selected from the group consisting of alkyl, acyl, or $-COC(R^{14})=N-OR^{15}$ wherein R^{14} is aryl or heteroaryl which optionally links (e) to the linker, and R^{15} is -(alkylene)-$COOR^{16}$ wherein R^{16} is hydrogen or a covalent bond that optionally links (e) to the linker or R^{13} is a covalent bond that links (e) to the linker provided that only one of R^{12}, R^{13}, R^{14} or R^{15} links said moiety to said linker;

L" is an optionally substituted vancomycin moiety or an aglycon derivative of an optionally substituted vancomycin moiety, wherein L" is attached to the linker at a position selected from the group consisting of the carboxy terminus, the amino terminus, the dihydroxyphenyl ring, the saccharide amino group and the aglycone hydroxy terminus; and

X' is a linker of the formula:

$$-X^a-Z^a-(Y^a-Z^a)_{m'}-X^a-$$

wherein

m' is an integer of from 0 to 20;

X^a at each separate occurrence is selected from the group consisting of -O-, -S-, -NR'-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR'-, -NR'C(O)-, C(S), -C(S)O-, -C(S)NR'-, NR'C(S)-, and a covalent bond;

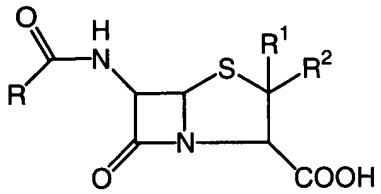
Z^a at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, and a covalent bond;

each Y^a at each separate occurrence is selected from the group consisting of -O-, -C(O)-, -OC(O)-, -C(O)O-, -NR'-, -S(O)n-, -C(O)NR'-, -NR'C(O)-, -NR'C(O)NR'-, NR'C(S)NR' -C(=NR')-NR'-, -NR'-C(=NR')-, -OC(O)-NR'-, -NR'-C(O)-O-, -P(O)(OR')-O-, -O-P(O)(OR')-, $-S(O)_nCR'R"-$, $-S(O)_n-NR'-$, $-NR'-S(O)_n-$, -S-S-, and a covalent bond; where *n* is 0, 1, or 2; and

R' and R" at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic;

provided, that when L" is a vancomycin moiety attached via its carboxyl group to the linker, then L' is not a cefalexin moiety attached to the linker via acylation of its α-amino group.

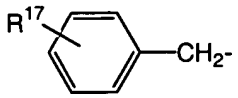
42. (Withdrawn) The compound of Claim 41, wherein the β-lactam moiety has the formula:

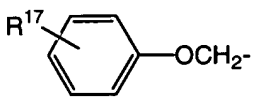


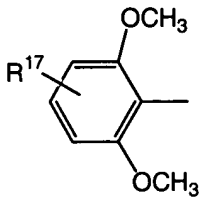
wherein:

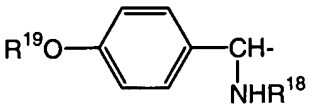
R^1 and R^2 are methyl; and

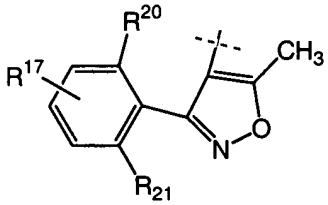
R is selected from the group consisting of:

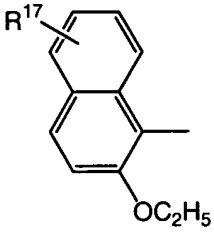
(i) 

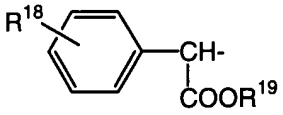
(ii) 

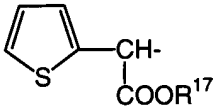
(iii) 

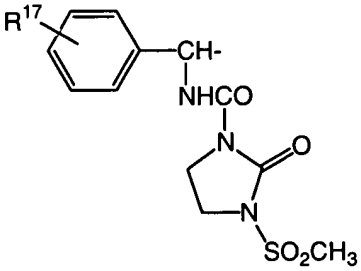
(iv) 

(v) 

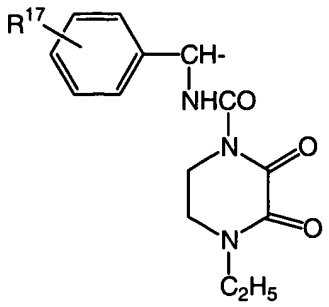
(vi) 

(vii) 

(viii) 

(ix) 

and

(x) 

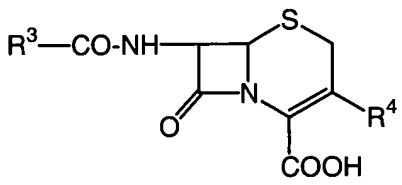
wherein:

R^{17} is a covalent bond that links the β-lactam moiety to a linker;

one of R^{18} and R^{19} is hydrogen and the other is a covalent bond that links the β-lactam moiety to a linker, and

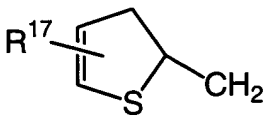
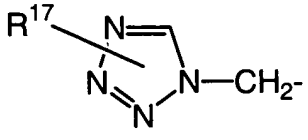
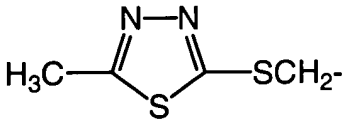
R^{20} and R^{21} are independently selected from the group consisting of hydrogen and chloro.

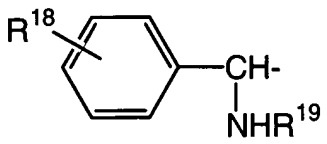
43. (Previously Presented) The compound of Claim 41, wherein L' is a moiety of the formula:

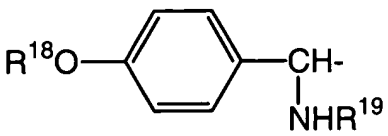


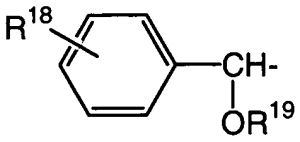
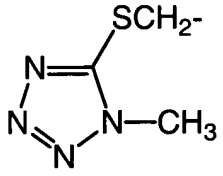
where:

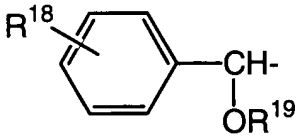
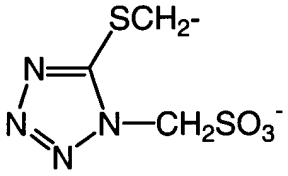
R^3 and R^4 are selected from the group consisting of:

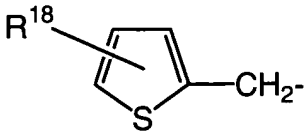
	R^3	R^4
(i)		$-CH_2OCOCH_3$
(ii)		

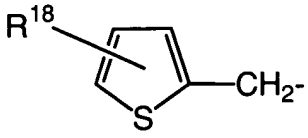
(iii)  $-CH_3$

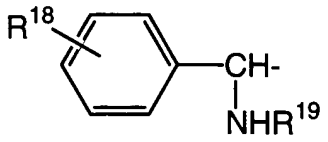
(iv)  $-CH_3$

(v)  

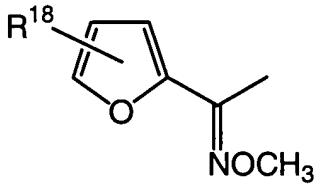
(vi)  

(vii)  $-CH_2OCONHR^{19}$

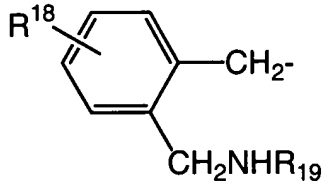
(viii)  $-CH_2OCOCH^3$

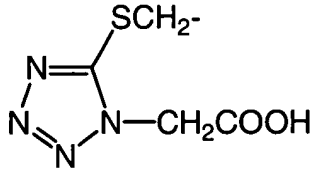
(ix) 

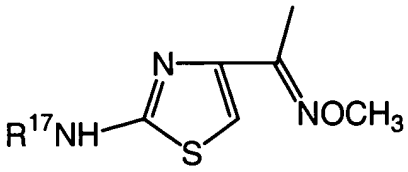
-Cl

(x) 

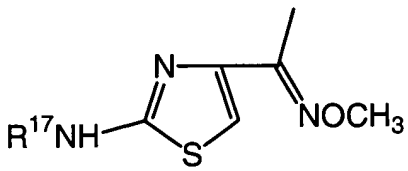
$-CH_2OCONHR^{19}$

(xi) 



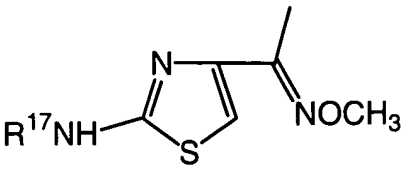
(xii) 

$-CH_2OCOCH_3$

(xiii) 

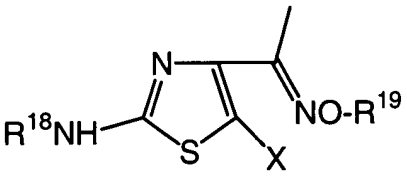
$-CH_2OCH_3$

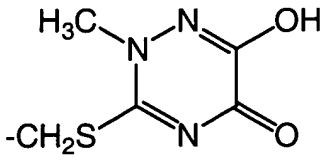
(xiv)



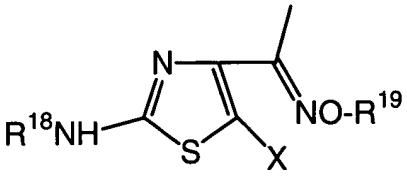
-H

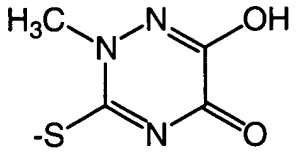
(xv)





(xvi)





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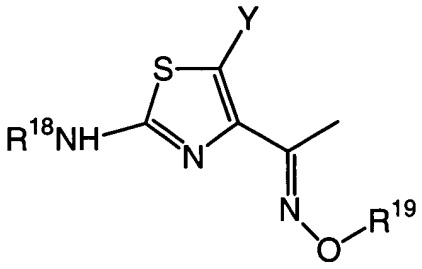

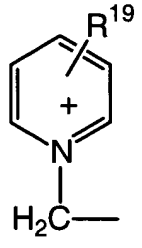

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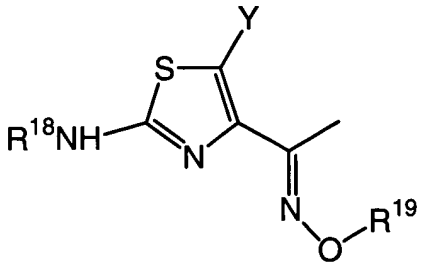
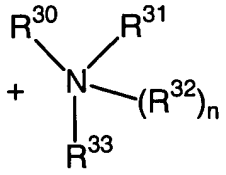
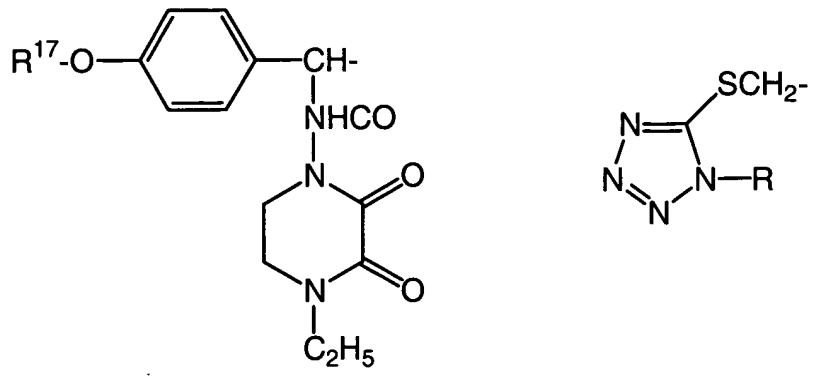
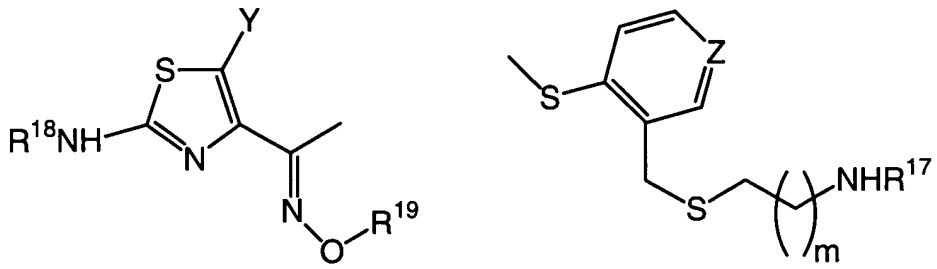




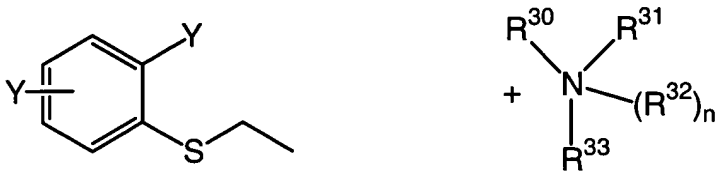
(xix)



(xx)



(xi)



wherein:

R is alkyl;

R^{17} is a covalent bond that links the L' moiety to the linker;

R^{18} and R^{19} are hydrogen or alkyl;

R^{30} and R^{31} are, independently of each other, hydrogen or alkyl; or together with the nitrogen atom to which they are attached form a heterocycloamino group;

R^{32} is alkyl;

R^{33} is alkylene;

X is halo;

Y is hydrogen or halo;

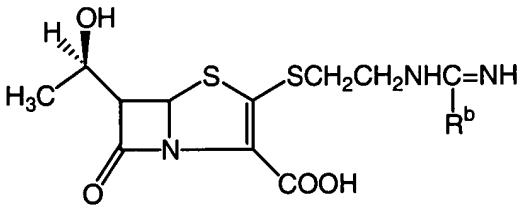
Z is CH or N;

m is an integer from 1 to 5;

n is 0 or 1;

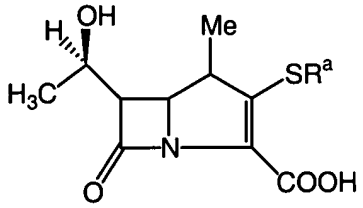
and further wherein one of R^{18}, R^{19}, R^{30}, R^{31}, R^{32} and R^{33} is a covalent bond that links the L' moiety to the linker.

44. (Withdrawn) The compound of Claim 41, wherein the β-lactam moiety has the formula:



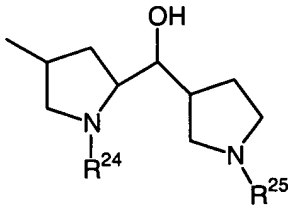
wherein R^b is a covalent bond linking the β-lactam moiety to the linker.

45. (Withdrawn) The compound of Claim 41, wherein the β-lactam moiety has the formula:

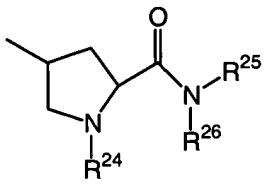


wherein R^a is selected from the group consisting of:

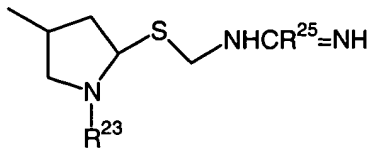
(i)



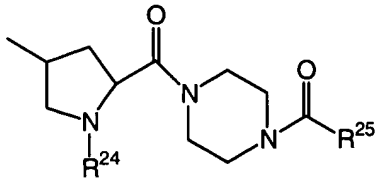
(ii)



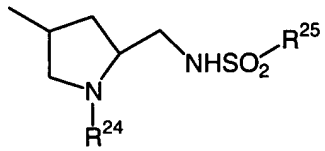
(iii)



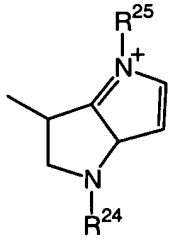
(iv)



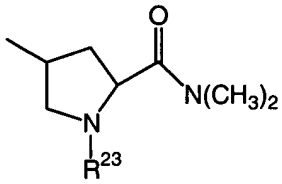
(v)



(vi)



(vii)



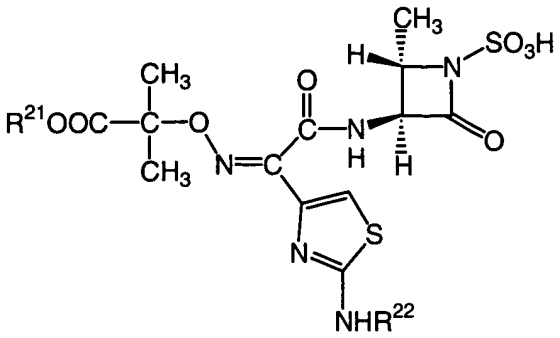
wherein:

R^{23} is a covalent bond that links the β-lactam moiety to the linker;

one of R^{24} and R^{25} is hydrogen, alkyl, substituted alkyl, or aralkyl, and the other is a covalent bond that links the β-lactam moiety to the linker; and

R^{26} is alkyl.

46. (Withdrawn) The compound of Claim 41, wherein the β-lactam moiety has the formula:



wherein one of R^{21} and R^{22} is hydrogen and the other links the β-lactam moiety to the linker.

49. (Previously Presented) The compound according to Claim 41 wherein L" is a vancomycin moiety which is attached to the linker at the saccharide amino group of the vancomycin moiety.

50. (Previously Presented) The compound according to Claim 41, wherein L" is a vancomycin moiety which is attached to the linker at the amino terminus of the vancomycin moiety.

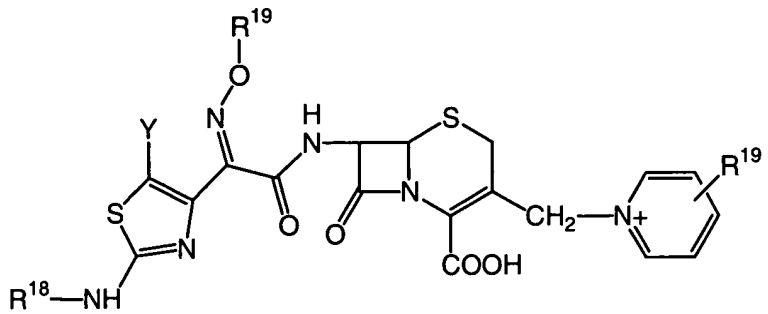
51. (Previously Presented) The compound according to Claim 41, wherein L" is a vancomycin moiety which is attached to the linker at the carboxy terminus of the vancomycin moiety.

53. (Previously Presented) A compound of the formula:

L'–X'–L"

or a pharmaceutically acceptable salt thereof; wherein

L' is a moiety of the formula:



wherein

Y is selected from the group consisting of hydrogen and halogen;

R^{18} and R^{19} are selected from the group consisting of hydrogen or alkyl provided that one of R^{18} and R^{19} is a covalent bond which links the L' moiety to the linker; and

L" is a vancomycin moiety, wherein L" is attached to the linker at a position selected from the group consisting of the carboxy terminus, the amino terminus, the dihydroxyphenyl ring and the saccharide amino group of the vancomycin moiety; and

X' is a linker of the formula:

$$-X^a-Z^a-(Y^a-Z^a)_{m'}-X^a-$$

wherein

m' is an integer of from 0 to 20;

X^a at each separate occurrence is selected from the group consisting of -O-, -S-, -NR'-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR'-, -NR'C(O)-, C(S), -C(S)O-, -C(S)NR'-, -NR'C(S)-, and a covalent bond;

Z^a at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, and a covalent bond;

each Y^a at each separate occurrence is selected from the group consisting of -O-, -C(O)-, -OC(O)-, -C(O)O-, -NR'-, -S(O)n-, -C(O)NR'-, -NR'C(O)-, -NR'C(O)NR'-, NR'C(S)NR'-, -C(=NR')-NR'-, -NR'-C(=NR')-, -OC(O)-NR'-, -NR'-C(O)-O-, -P(O)(OR')-O-, -O-P(O)(OR')-, $-S(O)_nCR'R"-$, $-S(O)_nNR'-$, $-NR'-S(O)_n-$, -S-S-, and a covalent bond; where *n* is 0, 1 or 2; and

R' and R" at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic.

54. (Previously Presented) The compound according to Claim 53, wherein Y is halogen.

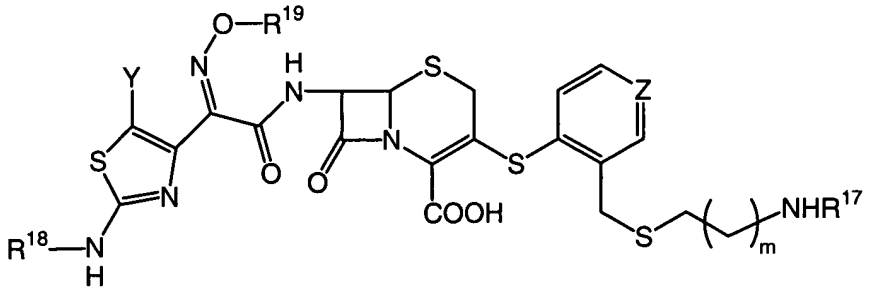
55. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of any of Claims 41-46, 49-51, 53, 54, 57 or 58.

57. (Withdrawn) A compound of the formula:

L'–X'–L"

or a pharmaceutically acceptable salt thereof; wherein

L' is a moiety of the formula:



wherein

Y is selected from the group consisting of hydrogen and halogen;

Z is CH or N;

R^{17} is a covalent bond that links the L' moiety to the linker;

R^{18} and R^{19} are selected from the group consisting of hydrogen or alkyl;

m is an integer from 1 to 5;

L" is a vancomycin moiety, wherein L" is attached to the linker at a position selected from the group consisting of the carboxy terminus, the amino terminus, the dihydroxyphenyl ring and the vancosamine amino group of the vancomycin moiety; and

X' is a linker of the formula:

$$-X^a-Z^a-(Y^a-Z^a)_{m'}-X^a-$$

wherein

m' is an integer of from 0 to 20;

X^a at each separate occurrence is selected from the group consisting of -O-, -S-, NR'-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR'-, NR'C(O)-, C(S), -C(S)O-, -C(S)NR'-, NR'C(S)-, and a covalent bond;

Z^a at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, and a covalent bond;

each Y^a at each separate occurrence is selected from the group consisting of

-O-, -C(O)-, -OC(O)-, -C(O)O-, -NR'-, -S(O)n-, -C(O)NR'-, -NR'C(O)-, -NR'C(O)NR'-, -NR'C(S)NR'-, -C(=NR')-NR'-, -NR'-C(=NR')-, -OC(O)-NR'-, NR'-C(O)-O-, -P(O)(OR')-O-, -O-P(O)(OR')-, $-S(O)_nCR'R"-$, $-S(O)_n-NR'-$, $-NR'-S(O)_n-$, -S-S-, and a covalent bond; where *n* is 0, 1 or 2; and

R' and R" at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic.

58. (Withdrawn) The compound according to Claim 57, wherein Y is halogen.

Application No.: 09/457,926
Attorney Docket No.: 09210.0004

VIII. Evidence Appendix to Appeal Brief Under Rule 41.37(c)(1)(ix)

No evidence, other than the references cited by the Office, are being relied on by Appellants in the appeal.